(a) providing at least one strand of the DNA as a single-stranded template primed with a set of oligonucleotide primers, each of which primers comprises a mass label cleavably attached to an oligonucleotide primer base sequence for hybridising to a single-stranded DNA template to form a primed template, wherein each mass label is cleavable from the primer in a mass spectrometer, uniquely resolvable in relation to every other mass labels in the set by mass spectrometry and identifies the oligonucleotide primer base sequence; and

(b) generating a population of fragments of said DNA from the and each template by contacting the and each template in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the and each template for forming a second strand of DNA complementary to the and each template, wherein the population comprises at least one series of DNA fragments, the or each series containing all possible lengths of a second strand of DNA complementary to the or each template;

wherein the feature of each fragment determined by each mass label relates to a nucleotide or nucleotide sequence at one end of each fragment, so that each nucleotide is related to a position in the template associated with the mass label so as to deduce the sequence of the or each template in order to characterise the DNA.

REMARKS

With the replacement of claims 25 and 26 with claims 27 and 28, claims 1-24, 27 and 28 are pending.

Applicants submit that the amendment to the claims would not narrow the scope of the amended claim limitations. For instance, the replacement of "DNA fragments" with "fragments of said DNA" in claims 1 and 2 would not narrow the scope of the claim limitation because, before the amendment, one skilled in the art would have known that "DNA fragments" refers to the fragments of the DNA being characterized. Similarly, the deletion of "sufficient" from claims 3-12 would not result in narrowing of the claim limitation because one skilled in the art would have known that "nucleotides sufficient for hybridising to the template" necessarily means nucleotides that can hybridise to the template. The replacement of "reaction zones" with "reaction vessels" would not narrow the scope of the claim limitation because one skilled in the art would have known from the disclosure of the specification, e.g. the paragraph bridging pages 25 and 26 and the last part of claim 4 as filed, that "reaction zones" refers to reaction vessels where the polymerization is conducted. The replacement of "unpolymerized nucleotides" with "unincorporated nucleotides" would not result in narrowing of the scope of the claim limitation because "unpolymerized" and "unincorporated" are interchangeable in this context.

Abstract

The specification was objected to for lacking an abstract. The objection is rendered moot with an abstract from the PCT application attached (see WO 99/02728).

Claim Rejection — 35 U.S.C. 101

Claims 25 and 26 were rejected for being drawn to a use without setting forth any method steps. Claims 25 and 26 have been replaced with claims 27 and 28 which recite method steps.

Claim Rejections — 35 U.S.C. 112, Second Paragraph

Responses to the indefinite rejections are discussed below using the labeling system of the Office Action. Applicants respectfully traverse the rejections.

b. Claims 1-20, 25 and 26 were rejected for a lack of method steps for DNA characterization. Claim 1 has been amended to recite how the DNA in the preamble of claim 1 is characterized with the steps recited in claim 1.

c. Claim 2 has been amended to state that the steps recited in claim 2 are carried out before step (i) of claim 1.

d. Claims 3-25 were rejected because of "sufficient". The word "sufficient" has been deleted.

e. Claims 3-25 were rejected because of "capable of" in the clause, "the nucleotide of each probe comprises a modified nucleotide which is capable of polymerizing to the second strand of DNA". Applicants submit that the clause is not indefinite because a person skilled in the art would understand that this clause means that polymerization of the modified nucleotide **of each probe** to the second strand of DNA is only optional, not required. The person skilled in the art would know that the clause requires that each probe comprises the modified nucleotide being able to polymerize to the second strand of DNA.

The method claims should not be indefinite merely because actual polymerization of the modified nucleotide **of each probe** to the second strand of DNA is optional because the person skilled in the art would understand that the probes could actually polymerize under the right condition.

f. Claims 6 and 7 were rejected because of the term "reaction zones". The term has been replaced with "reaction vessels" because one skilled in the art would have known that "reaction zones" refers to separate reaction vessels where formation of DNA fragments complementary to the DNA template is conducted. As described in the paragraph bridging pages 25 and 26, after Sanger ladders are generated in separate reaction vessels, the reaction products can be pooled (also see the last part of claim 4 as filed).

The Office Action asserted that the term "reaction zones" lacks antecedent basis. Applicants respectfully disagree. Applicants submit that "the reaction zones" in line 8 of claim 6 has proper antecedent basis on "four separate reaction zones" in line 4 of claim 6. The limitation, "four separate reaction zones" in line 4 of claim 6, requires no antecedent basis in claim 1. Similarly, "each set in a separate reaction zone" in line 5 of claim 7, coupled with the recitation that there are four sets of templates in line 2, provides proper antecedent basis to "the reaction zones" in line 9 of claim 8.

g. The phrase "removing unpolymerized nucleotides" does not require any antecedent basis because it is the first time that the term, "unpolymerized nucleotides", is mentioned in claim 9. The term "unpolymerized" has been replaced with "unincorporated" because "unpolymerized" and "unincorporated" are interchangeable in the context. Applicants also disagree with the Examiner regarding the replacement of "capable of

polymerizing" with "hybridizing" because the relevant method step concerns the optional polymerization of the nucleotide to form a complementary DNA, i.e. not just the hybridization of the nucleotide to the template.

h. Applicants have inserted "nucleotide" before "sequences" in "all combinations of sequences" in claims 9, 10 and 13. It would have been clear that "all combinations of nucleotide sequences" refers to all possible combinations of nucleotide sequences. For instance, for probes having a common length of 6 nucleotides, there are 4 x 4 x 4 x 4 x 4 x 4 nucleotide sequences present in the array.

i. To a person skilled in the art, it should have been clear that the clause, "modified nucleotide which is capable of ligating to the second strand of DNA", recites a characteristic of the modified nucleotide.

j. In the phrase "all possible oligonucleotides of the common length 1", "l" is one of the alphabets, not the numeral one (see paragraph 2 on page 12 of the PCT publication). The phrase does not mean that the oligonucleotides have a common length of **one** nucleotide. To make it more clear, "l" has been replaced with "L".

k. To make it more clear, "is relatable to" has been replaced with "identifies". The claim limitation, "the mass label cleavably attached to each primer is relatable to the variable sequence, which variable sequence is relatable to the particular template", means that a specific mass label of the primer corresponds to a specific variable sequence of the primer, so that which mass label corresponds to which variable sequence of the primer is known before the method of claim 13 is carried out. In other words, the mass label helps identify the variable sequence of the primer. From the identity of the mass label, a person

conducting the method of claim 13 would know the variable sequence of the primer. Since the primer hybridises to one of the templates, by knowing the variable sequence of the primer hybridised, the person would know the nucleotide sequence of a portion of the template.

l. Applicants submit that "a corresponding mass label" in step (e) of claim 21 or 22 is not indefinite because a person skilled in the art would understand that each probe is attached to a mass label that corresponds to the probe so that the person conducting the method of claim 21 or 22 would know which mass label corresponds to which probe. Similarly, "to relate its corresponding nucleotide sequence" in step (h) of claim 21 or 22 is not indefinite because the person skilled in the art would understand that the nucleotide sequence of the probe is known and the mass label that attaches to the probe is also known, so that which mass label corresponds to which nucleotide sequence is known. In other words, "its corresponding nucleotide sequence" in step (h) refers to the nucleotide sequence of the probe that corresponds to the mass label. To make it more clear, steps (e) and (h) of claims 21 and 22 have been amended.

m. Applicants have inserted "in order to characterise the DNA" at the end of claims 21-24. The amended claims do recite steps for DNA characterization.

n. Claim 27 replaces claim 25. The terms "relatable" and "corresponding" are not used in claim 27.

o. Similarly, claim 26 has been replaced with claim 28. The last step of claim 28 recites the term "relates". The term "relates" should not render claim 28 indefinite because, from the identity of the terminating nucleotide or oligonuclotide determined from

the mass label, and from the length of the fragment, the nucleotide sequence of the DNA can be deduced.

p. Claims 25 and 26 have been replaced with claims 27 and 28, which are drawn to two methods with the recitation of method steps.

Withdrawal of the rejections is requested.

Claim Rejections — 35 U.S.C. 102/103

I. Claim 1 was rejected as lacking novelty or obvious over Southern (WO95/04160). Applicants respectfully traverse the rejection.

Southern broadly discloses a method of labeling an analyte molecule with a cleavable tag linked to the analyte molecule at a designated position, wherein the tag has one or more reporter groups (see page 1, lines 23-36). Southern applies the method to sequence a nucleic acid (page 15, line 20 to page 16, line 9) and to sequence multiple nucleic acid templates (page 17) or to do fingerprinting of DNA (page 18). Southern differs from claim 1 at least in not teaching a step of separating the DNA fragments on the basis of their length.

In Southern's method, a moderately large labelled nucleic acid template is hybridised with an array of short oligonucleotide probes under very stringent hybridisation conditions. The Office Action argues that the positioning of the probes at discrete locations on the array corresponds to 'separating fragments on the basis of their length" because determination of the location at which the labelled large nucleic acid template hybridises determines the lenth of the probe. However, Southern's method does not determine the

length of the labelled template, which corresponds to the DNA being sequenced in the claimed method. In Southern's method, the length of the template must be known in advance, at least to the extent that it must be shorter than an upper limit. This upper limit is determined by the size of the array and the length of the subsequences determined. This is because, in order to infer the sequence of the template from its subsequences, it is necessary to know how likely it is that any subsequence will occur in the sequence of the known length (see Table 3 on page 23 of Southern). This allows statistical measurement of confidence in the inferred sequence to be determined. In Southern's method, the length of the labelled fragment is not measured since they must be known in advance to even start analyzing the labelled fragment. Therefore, in Southern's method, there is no step of separating the fragments on the basis of their length. In contrast, in the claimed method, it is the differences in length between the fragments of the template that allow their separation.

Southern also discloses a method in which a primer is hybridised to a nucleic acid template. Labelled probe oligonucleotides are then ligated to the primer. The labels are detached and detected, and the probe is unblocked so that further cycles of probe ligation and detection can be conducted. This method of Souther relies on knowing in advance a primer sequence. The sequence is then determined by identifying sequences of the predetermined length in steps along the template by successive ligation of probes. There is no separation of template fragments on the basis of their length in this method of Southern. The position of oligonucleotide subsequences is inferred from the number of cycles of ligation and the measurements that have already taken place.

Since Southern fails to teach every limitation of claim 1, Southern fails to anticipate claim 1.

There would have been no motivation or reason for modifying Southern's method by incorporating a step of separating template fragments on the basis of their length. As a result, applicants submit that claim 1 would not have been obvious over Southern.

Withdrawal of the rejections of Southern is requested.'

II. Claims 2-18 and 20-26 were rejected as obvious over Southern (WO95/04160) in view of Ness (US 6,027,890) and Alberts (Molecular Biology of the Cell, page 298, 1994). Applicants respectfully traverse the rejection.

The combination of these references does not indicate specifically how a probe should be labelled and used in order that the multiple labelled probes could be used simultaneously to sequence many templates in parallel. Thus, applicants submit that the instant claims would not have been obvious over Southern in view of Ness and Alberts.

In addition, there would have been no motivation to combine Southern, Ness and Alberts. Southern actually teaches away from the methods disclosed by Ness and Alberts. Southern discloses that the advantage of its hybridisation based method is that it avoids a need to determine the length of the DNA. Southern also discloses that gel based methods, such as the electrophoretic and chromatographic method of Ness cannot support the same degree of parallelism or throughput as array based methods. Since Southern emphasizes the advantage of its hybridisation based method and the disadvantage of the gel based

methods of Ness and Alberts, one of ordinary skill in the art would not have been motivated to use the teachings of Ness and Alberts to modify Southern's method.

Withdrawal of the obviousness rejection of the instant claims over Southern in view of Alberts and Ness is requested.

III. Claim 19 was rejected as obvious over Southern in view of Smith (*Nature*, vol. 349, pp. 812-813, 1991) . Applicants respectfully traverse the rejection based on two reasons.

First, the literal combination of the teachings of Southern and Smith does not actually indicate how labelled probes should be used to distinguish multiple tempates.

Second, Southern actually teaches away from the method disclosed by Smith. There would have been no motivation to combine Southern and Smith. Southern discloses that the advantage of its hybridisation based method is that it avoids a need to determine the length of the DNA. Southern also discloses that gel based methods, such as the electrophoretic and chromatographic method of Smith, cannot support the same degree of parallelism or throughput as array based methods. Since Southern emphasizes the advantage of its hybridisation based method and the disadvantage of the gel based methods of Smith, one of ordinary skill in the art would not have been motivated to use the teachings of Smith to modify Southern's method.

Withdrawal of the obviousness rejection of the instant claims over Southern in view of Smith is requested.

Conclusion

With the above reasoning, applicants submit that the present application is in a condition of allowance. A Notice of Allowance is believed in order.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: King Lit Wong
King Lit Wong
Registration No. 37,500

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: October 15, 2001

APPENDIX

Pursuant to 37 CFR 1.121, a marked up copy of the amendment is shown below.

1. (Amended) A method for characterizing DNA, which comprises:

(i) providing a population of [DNA] fragments of said DNA, each fragment having cleavably attached thereto a mass label for identifying a feature of that fragment;

(ii) separating the fragments on the basis of their length;

(iii) cleaving each fragment in a mass spectrometer to release its mass label; and

(iv) determining each mass label by mass spectrometry to relate the feature of each fragment to the length of the fragment in order to characterize said DNA.

2. (Amended) A method according to claim 1, which further comprises the following steps before step (i):

(a) providing at least one DNA single-stranded template primed with a primer; and

(b) generating the population of [DNA] fragments of said DNA from the at least one template, wherein the population comprises at least one series of DNA fragments, the or each series containing all possible lengths of a second strand of DNA complementary to the or each template;

wherein the feature of each fragment determined by each mass label relates to a nucleotide or nucleotide sequence at one end of each fragment, so that each nucleotide is related to a position in the template associated with the mass label so as to deduce the sequence of the or each template.

3. (Amended) A method according to claim 2, wherein the series of DNA fragments is provided by contacting the template in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the template in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto and which is cleavably attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the modified nucleotide, and wherein each fragment is terminated with one of the probes.

4. (Amended) A method according to claim 2, wherein the at least one template is a plurality of templates and the series of DNA fragments is provided by contacting each template in a separate reaction vessel [zone] in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the template in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto and which is cleavably attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the modified nucleotide, wherein each fragment is terminated with one of the probes, and wherein each set of mass labels from each set of

four probes associated with each reaction vessel [zone] is different from the other sets of mass labels; and the fragments are pooled before step (ii).

5. (Amended) A method according to claim 2, wherein the at least one template is a plurality of templates and the series of DNA fragments is provided by contacting each template in a separate reaction vessel [zone] in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a probe containing only one of the four nucleotides for hybridising to the template, the nucleotide of which probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto, wherein each fragment is terminated with the probe and wherein either the primer or the modified nucleotide of the probe is cleavably attached to the mass label, which mass label is associated with the reaction vessel [zone] and uniquely resolvable in mass spectrometry from the mass label in the other reaction vessels [zones] for identifying the modified nucleotide used in the reaction vessel [zone]; and the fragments are pooled before step (ii).

6. (Amended) A method according to claim 2, wherein the at lease one template is a plurality of templates and the series of DNA fragments is provided by contacting the plurality of templates in each of four separate reaction vessels [zones] in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template

for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a probe containing in each of the reaction vessels [zones] only one of the four nucleotides for hybridising to the template, the nucleotide of which probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto, wherein each fragment is terminated with the probe and wherein the primer is cleavably attached to the mass label, which mass label is associated with the primer and uniquely resolvable in mass spectrometry from the mass labels associated with the other primers used in the reaction zone; and wherein each nucleotide from its corresponding reaction vessel [zone] is related to its position in the template.

7. (Amended) A method according to claim 2, wherein the at least one template is four sets of DNA single-stranded templates, each set comprising an identical plurality of DNA single-stranded templates and the series of DNA fragments is provided by contacting each set in a separate reaction vessel [zone] in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the templates for forming a second strand of DNA complementary thereto, wherein the mixture further comprises a probe containing in each of the reaction vessels [zones] only one of the four nucleotides for hybridising to the template, the nucleotide of which probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerization thereto, wherein each fragment is terminated with the probe and wherein each of the templates of the four sets is primed with a primer to which the mass

label is cleavably attached, which mass label which uniquely resolvable in mass spectrometry from the mass labels corresponding to the other templates and which is relatable to its respective template and its respective reaction vessel [zone], wherein the fragments are pooled before step (ii), and each nucleotide from its corresponding reaction zone is related to its position in the template.

8. (Amended) A method according to claim 2, wherein the at least one template is a plurality of templates and the series of DNA fragments is provided by contacting each set of templates in a separate reaction vessel [zone] in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the templates for forming a second strand of DNA complementary thereto, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the template in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto and which is cleavable attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the modified nucleotide, wherein each fragment is terminated with one of the probes, and wherein each set of mass labels from each set of four probes associated with each reaction vessel [zone] is different from the other sets of mass labels and, before step (ii), the fragments are pooled and the pooled fragments are sorted according to a sub-sequence having a common length of 3 to 5 bases adjacent to the primer to form an array of groups of sorted fragments, wherein each group is spatially separated from the other groups.

9. (Amended) A method according to claim 2, wherein the series of DNA fragments is provided by

(i) contacting the template in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(ii) removing unincorporated [unpolymerized] nucleotides;

(iii) unblocking the modified nucleotides; and

(iv) contacting the series of templates with an array of oligonucleotide probes, wherein each oligonucleotide probe has a nucleotide sequence of common length 2 to 6, all combinations of nucleotide sequences are present in the array, and wherein each probe is cleavably attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the nucleotide sequence.

10. (Amended) A method according to claim 2, wherein the at least one template is a plurality of primed DNA single-stranded templates, each at a unique concentration, and the series of DNA fragments is provided by

(i) contacting the templates in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the templates, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(ii) removing unincorporated [unpolymerised] nucleotides;

(iii) unblocking the modified nucleotides; and

(iv) contacting the series of templates with an array of oligonucleotide probes, wherein each oligonucleotide probe has a nucleotide sequence of common length 2 to 6, all combinations of nucleotide sequences are present in the array, and wherein each probe is cleavably attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the nucleotide sequence.

11. (Amended) A method according to claim 2, wherein the series of DNA fragments is provided by contacting the template in the presence of DNA ligase with a mixture of oligonucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, the oligonucleotides each having a common length in the range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L [1] for hybridising to the templates in

which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavable attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the modified oligonucleotide, and the series of fragments contains all possible lengths of the second strand of DNA of integer multiples of L [1], in which each fragment is terminated with one of the probes.

12. (Amended) A method according to claim 2, wherein the at least one template is a plurality of primed DNA single-stranded templates, each at a unique concentration, and the series of DNA fragments is provided by contacting the templates in the presence of DNA ligase with a mixture of oligonucleotides [sufficient] for hybridising to the templates for forming a second strand of DNA complementary to the templates, the oligonucleotides each having a common length in the range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L [1] for hybridising to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to the mass label, which mass label is uniquely resolvable in mass spectrometry for identifying the modified oligonucleotide, and the series of fragments contains all possible lengths of the second strand of DNA of integer multiples of L [1], in which each fragment is terminated with one of the probes.

13. (Amended Twice) A method according to claim 5, wherein the plurality of single-stranded templates is primed by hybridising to a known sub-sequence common to each of the templates an array of primers each comprising a base sequence containing a common sequence complementary to the known sub-sequence and a variable sequence of common length, in the range of 2 to 6, in which the array contains all possible nucleotide sequences of that common length and the mass label cleavably attached to each primer identifies [is relatable to] the variable sequence, which variable sequence identifies [is relatable to] the [particular] template to be sequenced.

21. (Amended) A method for characterising DNA, which comprises

(a) providing a primed DNA single-stranded template;

(b) contacting the template in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(c) removing unincorporated [unpolymerised] nucleotides;

(d) unblocking the modified nucleotides;

(e) contacting the series of templates with an array of oligonucleotide probes to form a series of fragments, each oligonucleotide probe having a nucleotide sequence of common length 2 to 6, and all combinations of sequences being present in the array, wherein each probe is cleavably attached to a [corresponding] mass label uniquely resolvable in mass spectrometry for identifying the nucleotide sequence;

(f) separating the fragments from one another on the basis of their length;

(g) cleaving each fragment to release its mass label; and

(h) determining each mass label by mass spectrometry to relate [its corresponding] a nucleotide sequence that corresponds to the mass label to a position in the template so as to deduce the sequence of the template in order to characterise the DNA.

22. (Amended) A method for characterising DNA, which comprises

(a) providing a plurality of primed DNA single-stranded templates, each at a unique concentration;

(b) contacting the templates in the presence of DNA polymerase with a mixture of nucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the templates, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the templates in which the nucleotide of each probe comprises a modified nucleotide which is capable of polymerising to the second strand of DNA but reversibly blocked to prevent further polymerisation thereto, wherein the step of contacting forms a series of templates containing all possible lengths of the second strand of DNA, each second strand terminated with one of the probes;

(c) removing unincorporated [unpolymerised] nucleotides;

(d) unblocking the modified nucleotides;

(e) contacting the series of templates with an array of oligonucleotide probes to form a series of fragments, each oligonucleotide probe having a nucleotide sequence of common length 2 to 6, and all combinations of sequences being present in the array, wherein each probe is cleavably attached to a [corresponding] mass label uniquely resolvable in mass spectrometry for identifying the nucleotide sequence;

(f) separating the fragments from one another on the basis of their length;

(g) cleaving each fragment to release its mass label; and

(h) determining the identity and amount of each mass label by mass spectrometry to relate [its corresponding] a nucleotide sequence of a probe that corresponds to the mass label to a position in its respective template so as to deduce the sequence of the template in order to characterise the DNA.

23. (Amended) A method for characterising DNA, which comprises

(a) providing a primed DNA single-stranded template;

(b) contacting the template in the presence of DNA ligase with a mixture of oligonucleotides [sufficient] for hybridising to the template for forming a second strand of DNA complementary to the template, the oligonucleotides each having a common length in the range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L [1] for hybridising to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is

capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a corresponding mass label uniquely resolvable in mass spectrometry for identifying the modified oligonucleotide, wherein the step of contacting forms a series of fragments containing all possible lengths of the second strand of DNA of integer multiples of L [1], each fragment terminated with one of the probes;

(c) separating the fragments from one another on the basis of their length;

(d) cleaving each fragment to release its mass label; and

(e) determining each mass label by mass spectrometry to relate its corresponding oligonucleotide to a position in the template so as to deduce the sequence of the template in order to characterise the DNA.

24. (Amended) A method for characterising DNA, which comprises

(a) providing a plurality of primed DNA single-stranded templates, each at a unique concentration;

(b) contacting the templates in the presence of DNA ligase with a mixture of oligonucleotides [sufficient] for hybridising to the templates for forming a second strand of DNA complementary to the templates, the oligonucleotides each having a common length in the range 2 to 6, wherein the mixture further comprises a set of probes containing all possible oligonucleotides of the common length L [1] for hybridising to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a corresponding mass label uniquely resolvable

in mass spectrometry for identifying the modified oligonucleotide, wherein the step of contacting forms a series of fragments containing all possible lengths of the second strand of DNA of integer multiples of L [1], each fragment terminated with one of the probes;

(c) separating the fragments from one another on the basis of their length;

(d) cleaving each fragment to release its mass label; and

(e) determining the identity and amount of each mass label by mass spectrometry to relate its corresponding oligonucleotide to a position in its respective template so as to deduce the sequence of the template in order to characterise the DNA.